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L8   ANSWER 1 OF 5  HCAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         2003:766786  HCAPLUS
DOCUMENT NUMBER:          140:55178
TITLE:                    Potentiating effect of distant sites in
                          non-phosphorylated cyclic peptide antagonists of the
                          Grb2-SH2 domain
AUTHOR(S):                Long, Ya-Qiu; Guo, Ribo; Luo, Juliet H.; Yang, Dajun;
                          Roller, Peter P.
CORPORATE SOURCE:         Shanghai Institutes for Biological Sciences, Shanghai
                          Institute of Materia Medica, State Key Laboratory of
                          Drug Research, Chinese Academy of Sciences, Shanghai,
                          201203, Peop. Rep. China
SOURCE:                   Biochemical and Biophysical Research Communications
                          (2003), 310(2), 334-340
                          CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER:                Elsevier Science
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Without the presence of a phosphotyrosyl group, a phage library derived
     non-phosphorylated cyclic peptide ligand of Grb2-SH2 domain attributed its
     high affinity and specificity to well-defined and highly favored
     interactions of its structural elements with the binding pocket of the
     protein.  We have disclosed a significant compensatory role of the Glu2-
     sidechain for the absence of the phosphate functionality on Tyr0 in the
     peptide ligand, cyclo(CH2CO-Glu2--Leu-Tyr0-Glu-Asn-Val-Gly-Met5+-Tyr-Cys)-
     amide (termed G1TE).  In this study, we report the importance of
     hydrophobic residue at the Tyr + 5 site in G1TE.  Both acidic and basic
     amino acid substitutes are disfavored at this position, and replacement of
     Met with β-tert-butyl-Ala was found to improve the antagonist
     properties.  Besides, the polarity of the cyclization linkage was
     implicated as important in stabilizing the favored binding conformation.
```

Oxidation of the thioether linkage into sulfoxide facilitated the binding to Grb2-SH2 markedly. Simultaneous modification of the three distant sites within G1TE provided the best agent with an IC50 of 220 nM, which is among the most potent non-phosphorous- and non-phosphotyrosine-mimic containing Grb2-SH2 domain inhibitors yet reported. This potent peptidomimetic provides a novel template for the development of chemotherapeutic agents for the treatment of erbB2-related cancer. Biol. assays on G1TE(Gla2-) in which the original residue of Glu2- was substituted by γ-carboxyglutamic acid (Gla) indicated that it could inhibit the interaction between activated GF receptor and Grb2 protein in cell homogenates of MDA-MB-453 breast cancer cells at the 2 μM level. More significantly, both G1TE(Gla2-) alone and the conjugate of G1TE(Gla2-) with a peptide carrier can effectively inhibit intracellular association of erbB2 and Grb2 in the same cell lines with IC50 of 50 and 2 μM, resp.

IT **637350-43-7 637350-44-8 637350-45-9 637350-46-0**

RL: BSU (Biological study, unclassified); BIOL (Biological study) (potentiating effect of distant sites in non-phosphorylated cyclic peptide antagonists of Grb2-SH2 domain)

RN 637350-43-7 HCAPLUS

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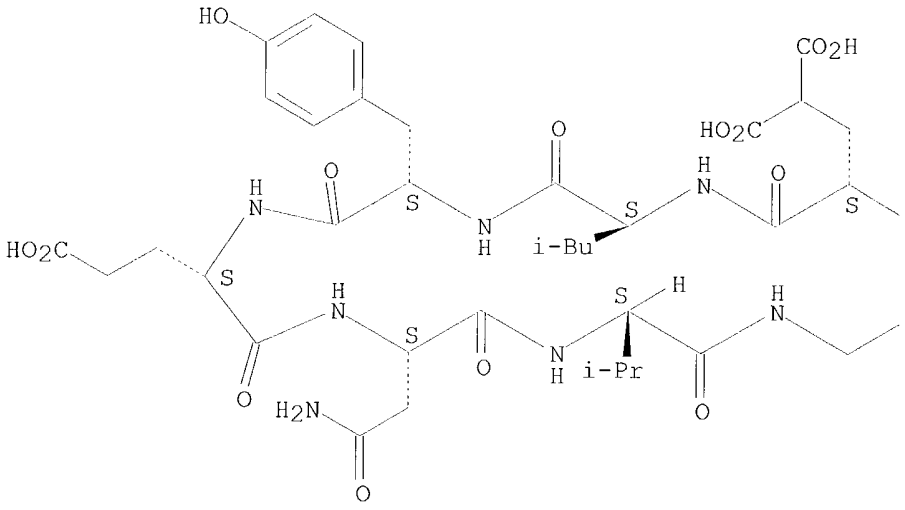
Absolute stereochemistry.

PAGE 1-A



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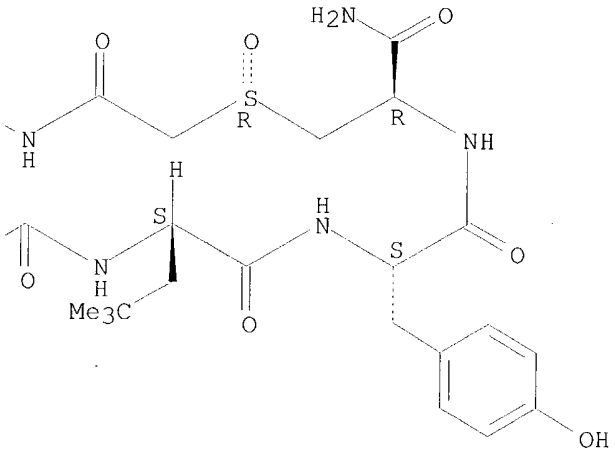

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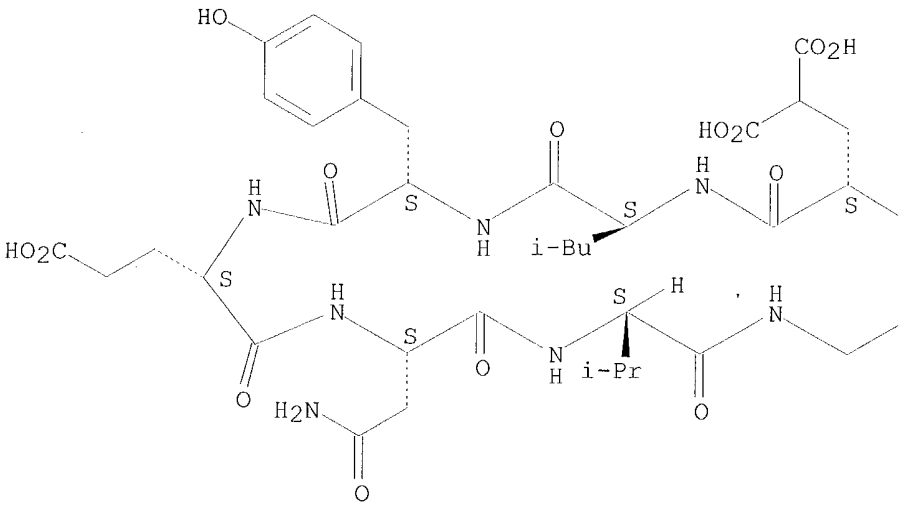
Absolute stereochemistry.

PAGE 1-A



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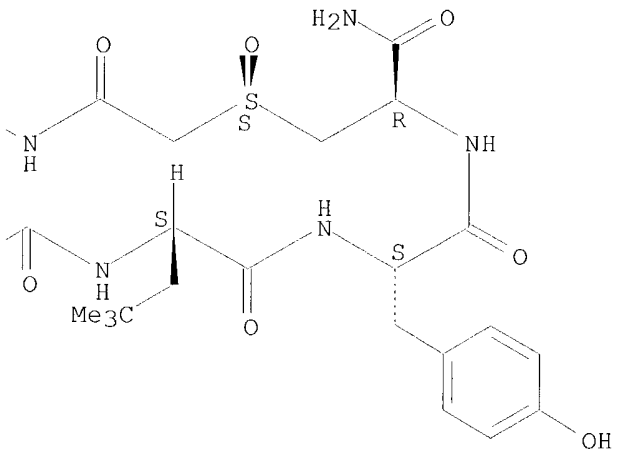

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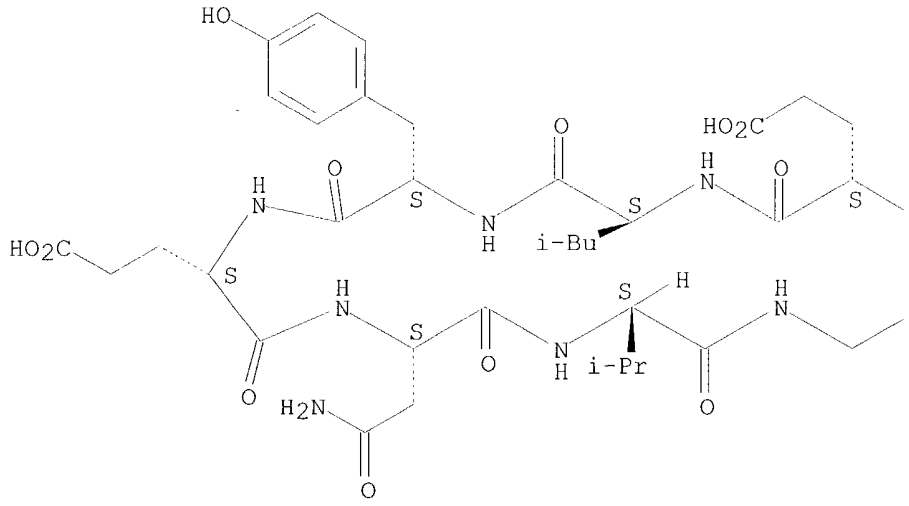
Absolute stereochemistry.

PAGE 1-A



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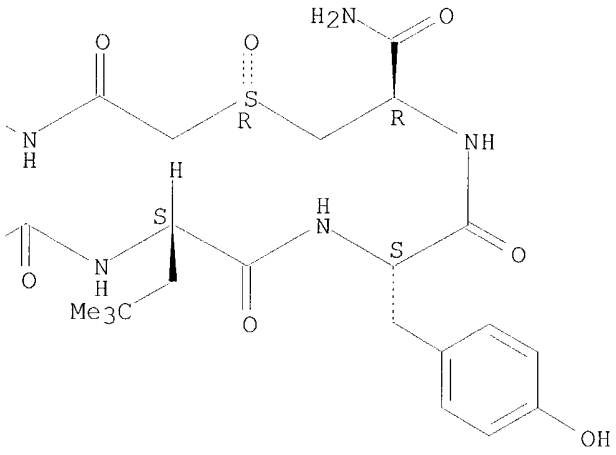

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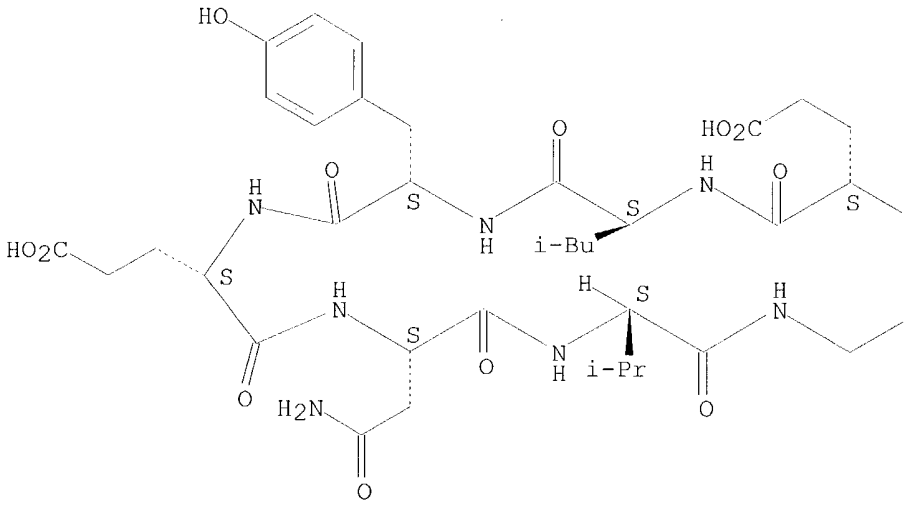
Absolute stereochemistry.

PAGE 1-A



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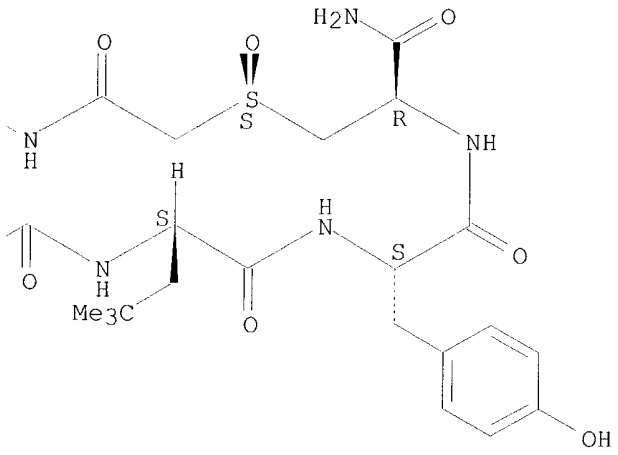

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L8 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:645686 HCAPLUS
DOCUMENT NUMBER: 140:122075
TITLE: Global optimization of conformational constraint on non-phosphorylated cyclic peptide antagonists of the Grb2-SH2 domain
AUTHOR(S): Long, Ya-Qiu; Lung, Feng-Di T.; Roller, Peter P.
CORPORATE SOURCE: Shanghai Institutes for Biological Sciences, Shanghai Institute of Materia Medica, State Key Laboratory of Drug Research, Chinese Academy of Sciences, Shanghai, 201203, Peop. Rep. China
SOURCE: Bioorganic & Medicinal Chemistry (2003), 11(18), 3929-3936
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Following our earlier work on a phage library derived non-phosphorylated thioether-cyclized peptide inhibitor of Grb2 SH2 domain, a series of small peptide analogs with various cyclization linkage or various ring size were designed and synthesized and evaluated to investigate the optimal conformational constraint for this novel Grb2-SH2 blocker. Our previous SAR studies have indicated that constrained conformation as well as all amino acids except Leu2 and Gly7 in this lead peptide, cyclo(CH2CO-Glu1-Leu-Tyr-Glu-Asn-Val-Gly-Met-Tyr-Cys10)-amide (termed G1TE), was necessary for sustenance of the biol. activity. In this study, in an effort to derive potent and bioavailable Grb2-SH2 inhibitor with minimal sequence, we undertook a systematic conformational study on this non-phosphorylated cyclic ligand by optimizing the ring linkage, ring configuration and ring size. The polarity and configuration of the cyclization linkage were implicated important in assuming the active conformation. Changing the flexible thioether linkage in G1TE into the

relatively rigid sulfoxide linkage secured a 4-fold increase in potency (4', IC50 = 6.5 μM). However, open chain, shortening or expanding the ring size led to a marked loss of inhibitory activity. Significantly, the introduction of ω-amino carboxylic acid linker in place of three C-terminal amino acids in G1TE can remarkably recover the apparently favorable conformation, which is otherwise lost because of the reduced ring size. This modification, combined with favorable substitutions of Gla for Glu1 and Adi for Glu4 in the resulting six-residue cyclic peptide, afforded peptide, with an almost equal potency ,(IC50 = 23.3 μM) relative to G1TE. Moreover, the lipophilic chain in ω-amino carboxylic acid may confer better cell membrane permeability to the peptide. These newly developed G1TE analogs with smaller ring size and less peptide character but equal potency can serve as templates to derive potent and specific non-phosphorylated Grb2-SH2 antagonists.

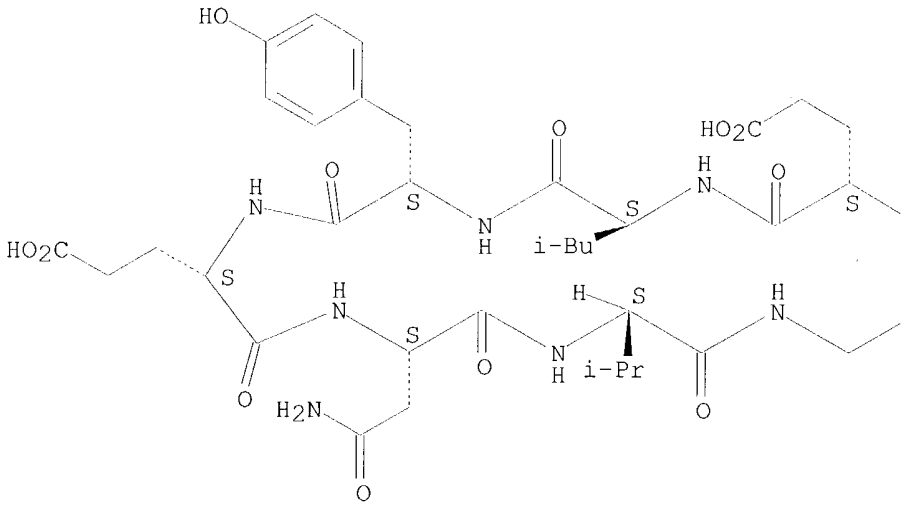
IT **282118-08-5DP**, stereoisomers
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(global optimization of conformational constraint on non-phosphorylated cyclic peptide antagonists of Grb2-SH2 domain)

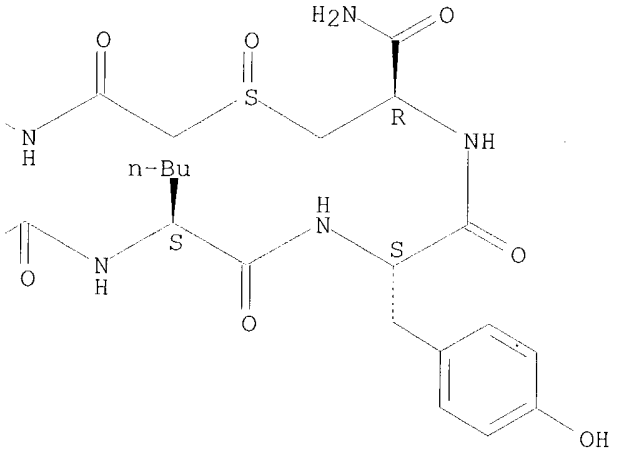
RN 282118-08-5 HCAPLUS

CN L-Cysteinamide, N-(mercaptoacetyl)-L-α-glutamyl-L-leucyl-L-tyrosyl-L-α-glutamyl-L-asparaginyl-L-valylglycyl-L-norleucyl-L-tyrosyl-, cyclic (1→10)-thioether, S-oxide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A





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L8 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:319477 HCAPLUS
DOCUMENT NUMBER: 138:287983
TITLE: Redox-stable, non-phosphorylated cyclic peptide inhibitors of SH2 domain binding to target protein, conjugates thereof, compositions, methods of synthesis, and use
INVENTOR(S): Roller, Peter P.; Long, Ya-Qiu; Lung, Feng-Di T.; King, C. Richter; Yang, Dajun
PATENT ASSIGNEE(S): The Government of the United States of America, USA
SOURCE: U.S. Pat. Appl. Publ., 10 pp., Cont.-in-part of Appl. No. PCT/US00/15201.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003078368	A1	20030424	US 2001-998350	20011130
WO 2000073326	A2	20001207	WO 2000-US15201	20000602
WO 2000073326	A3	20010525		

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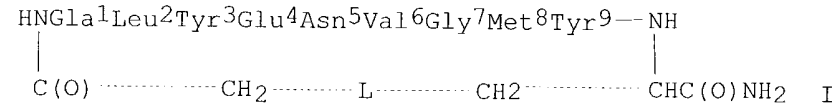

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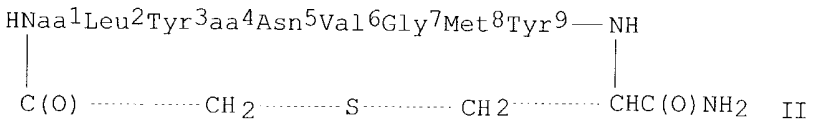


II

AB The invention provides I (L = S, SO, O, CH2; optionally, ≥1 of Tyr3, Glu4, Val6, Met8 and Tyr9 is modified). Also provided are compds. II [aa1 = Adi and aa4 = Glu, or each of aa1 and aa4 = Adi; L = S, SO, O, CH2; optionally, ≥1 of Tyr3, Val6, Met8 and Tyr9 is modified]. Compds. I and II (and their conjugates) bind to an SH2 domain in a protein comprising an SH2 domain, are non-phosphorylated, are redox-stable in vivo, and are characterized by an IC50 in vivo of less than about 4.0 < mM with respect to the SH2 domain in Grb2. Upon binding to the SH2 domain of Grb2, a compound as described above has a turn conformation. Also provided are a conjugate comprising a compound as described above and a carrier agent, a composition comprising (i) a compound or a conjugate as described above and (ii) a carrier, a method of inhibiting binding of an SH2 domain in a protein comprising an SH2 domain to a target protein in an animal, where the SH2 domain is contacted with a target protein-binding inhibiting effective amount of a compound or a conjugate as described above, and a method of synthesizing such conjugates. Thus, cyclo(CH2CO-Adi1-Leu2-Tyr3-Glu4-Asn5-Val6-Gly7-Met8-Tyr9-Cys)-amide was synthesized by the solid-phase method and showed IC50 = 3.45 ± 0.15 for binding affinity to the SH2 domain of Grb2.

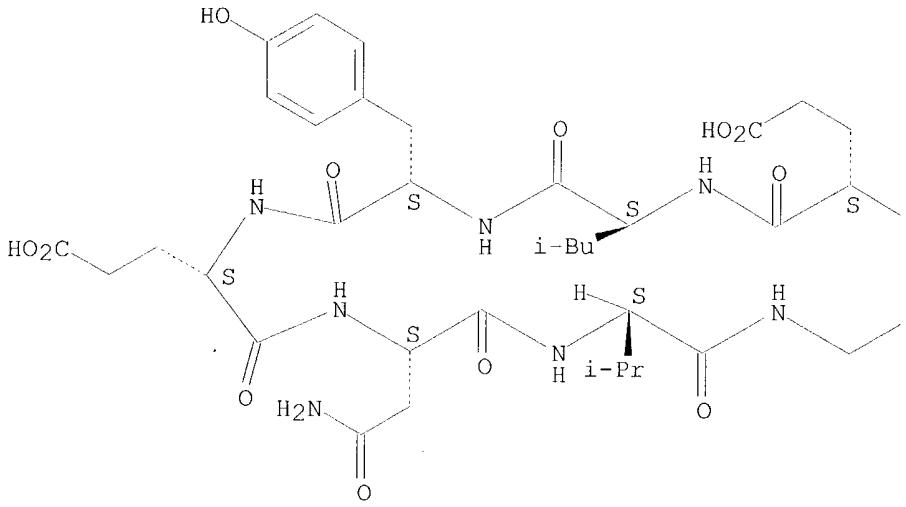
IT **282118-08-5P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of redox-stable, non-phosphorylated cyclic peptide inhibitors of SH2 domain binding to target protein)

RN 282118-08-5 HCAPLUS

CN L-Cysteinamide, N-(mercaptoacetyl)-L-α-glutamyl-L-leucyl-L-tyrosyl-L-α-glutamyl-L-asparaginyl-L-valylglycyl-L-norleucyl-L-tyrosyl-, cyclic (1→10)-thioether, S-oxide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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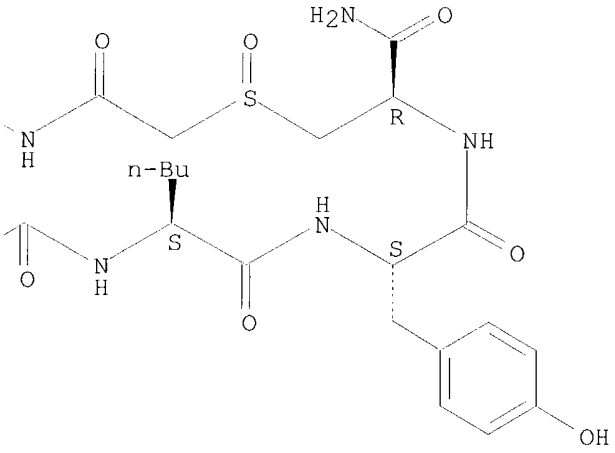

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RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of redox-stable, non-phosphorylated cyclic peptide inhibitors of SH2 domain binding to target protein)

RN 311791-05-6 HCAPLUS

CN L-Cysteinamide, 4-carboxy-N-(mercaptoacetyl)-L-α-glutamyl-L-leucyl-L-

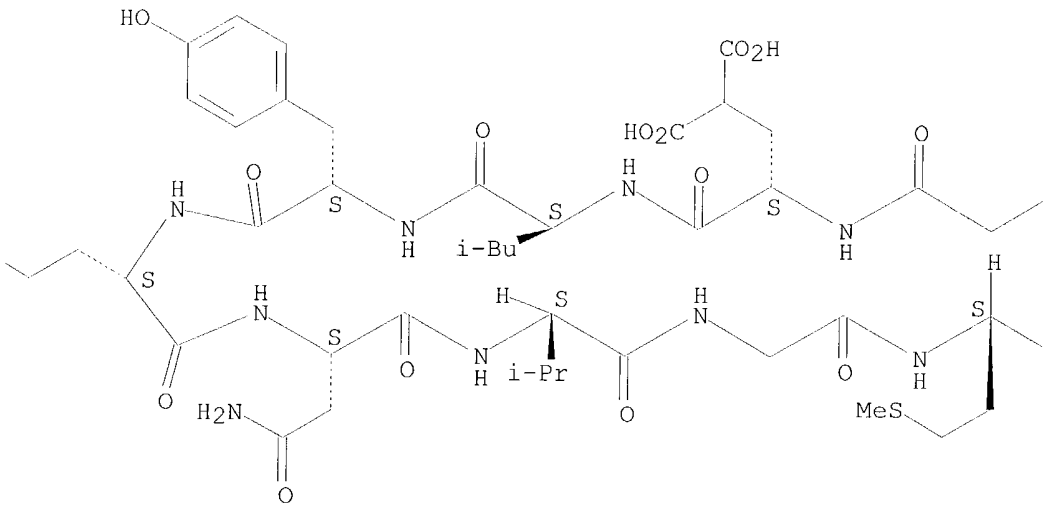
tyrosyl-L-α-glutamyl-L-asparaginyl-L-valylglycyl-L-methionyl-L-tyrosyl-, cyclic (1→10)-thioether, S-oxide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

HO_2C

PAGE 1-B



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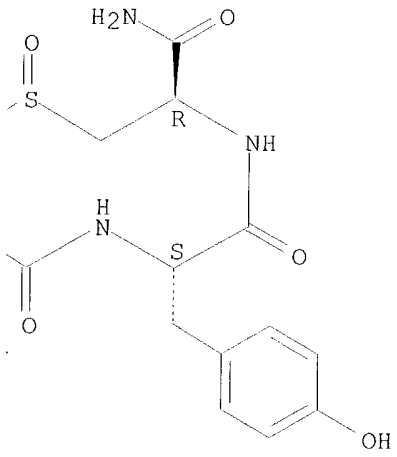

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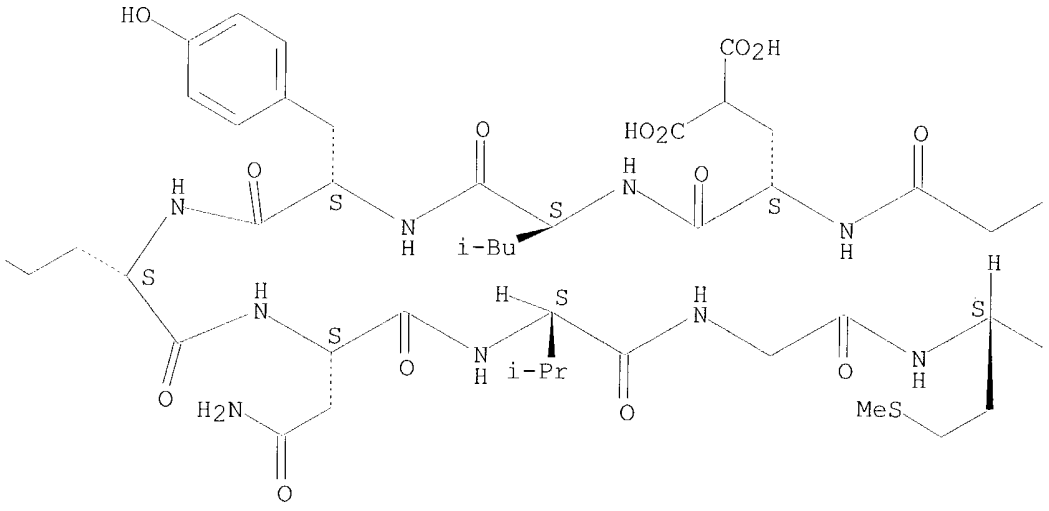
Absolute stereochemistry.

PAGE 1-A

PAGE 1-B



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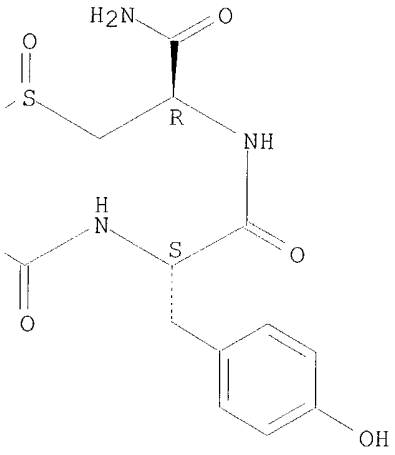

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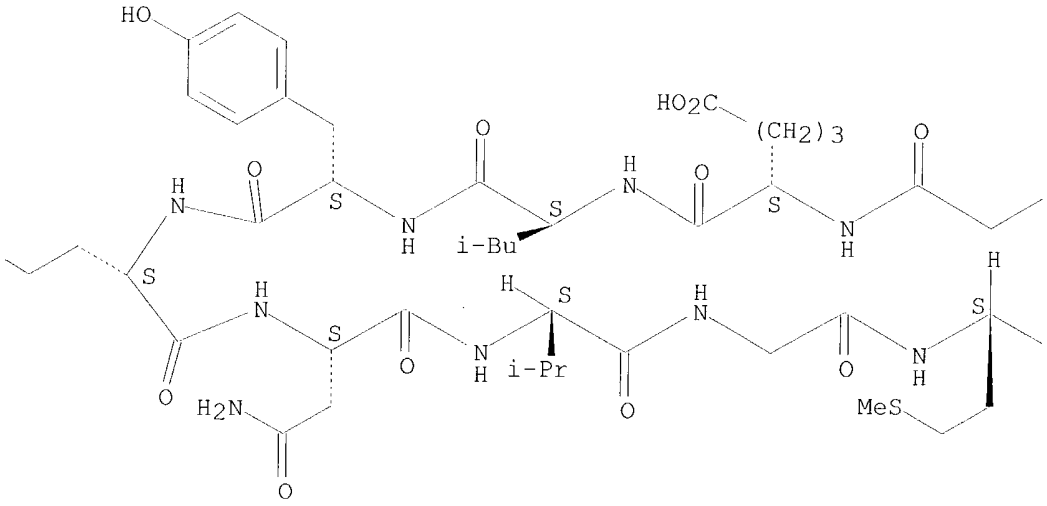
Absolute stereochemistry.

PAGE 1-A

HO_2C

PAGE 1-B



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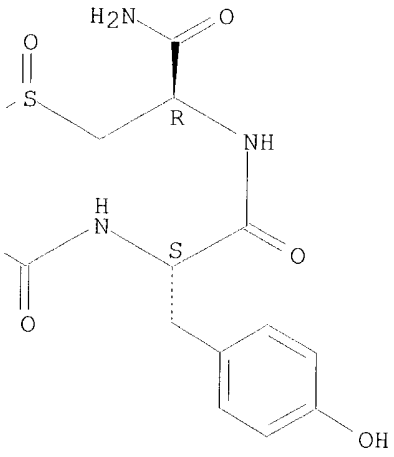

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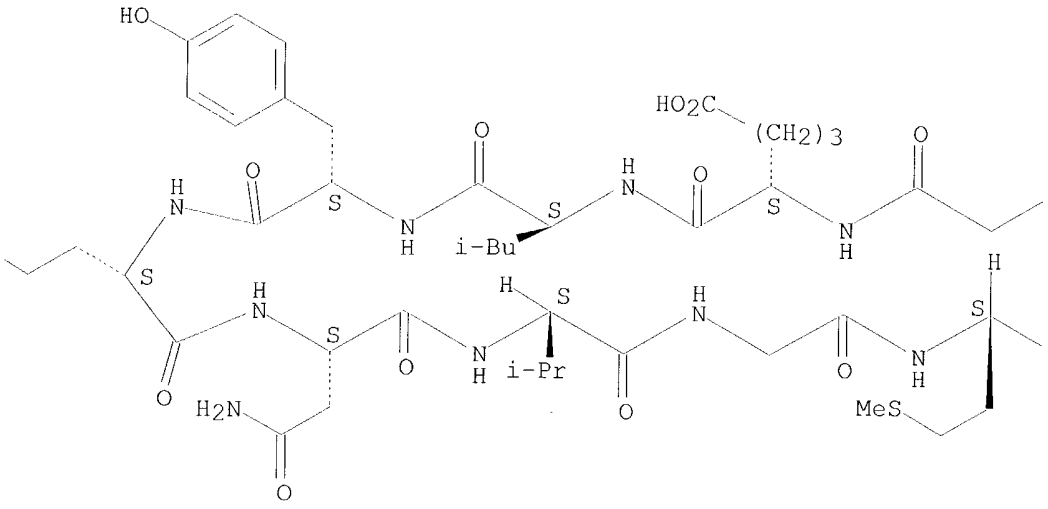
Absolute stereochemistry.

PAGE 1-A

PAGE 1-B



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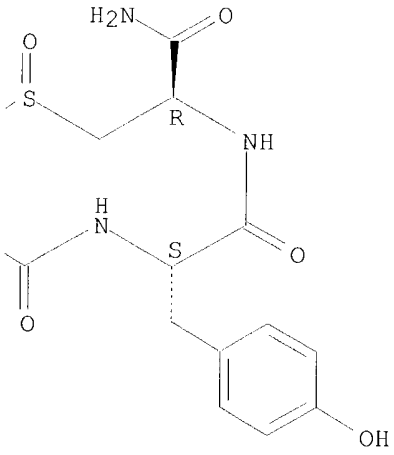

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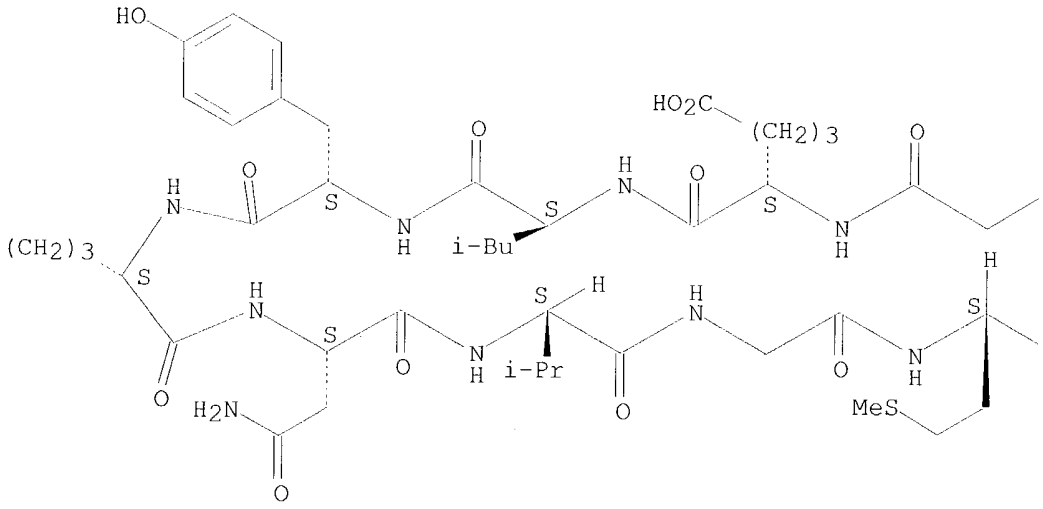
Absolute stereochemistry.

PAGE 1-A

PAGE 1-B



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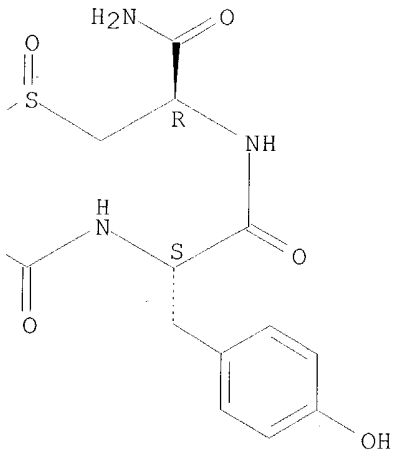

RN 311791-23-8 HCAPLUS
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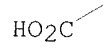
Absolute stereochemistry.

PAGE 1-A



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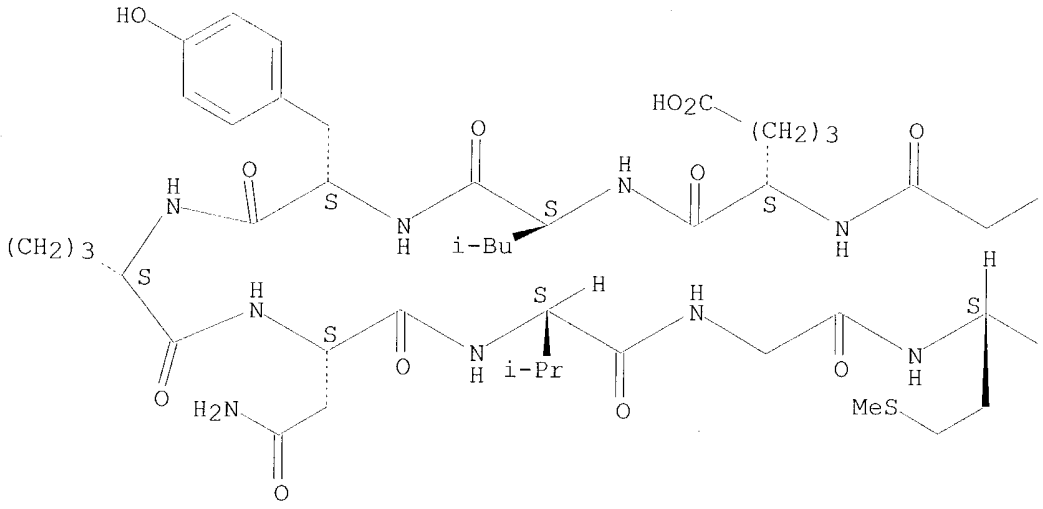

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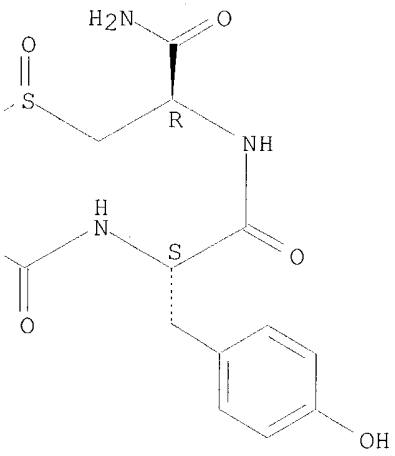

L8 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:861699 HCAPLUS
DOCUMENT NUMBER: 134:25345
TITLE: Redox-stable, non-phosphorylated cyclic peptide inhibitors of SH2 domain binding to target protein, conjugates thereof, compositions, methods of synthesis, and use
INVENTOR(S): Roller, Peter P.; Long, Ya-Qui; Lung, Feng-Di T.; King, C. Richter; Yang, Dajun

PATENT ASSIGNEE(S): Government of the United States of America, Represented by the Secretary, Department of Health and Human Services, USA
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000073326	A2	20001207	WO 2000-US15201	20000602
WO 2000073326	A3	20010525		

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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2003078368	A1	20030424	US 2001-998350	20011130

PRIORITY APPLN. INFO.: US 1999-137187P P 19990602
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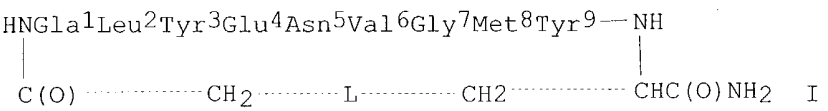
OTHER SOURCE(S): MARPAT 134:25345
GI



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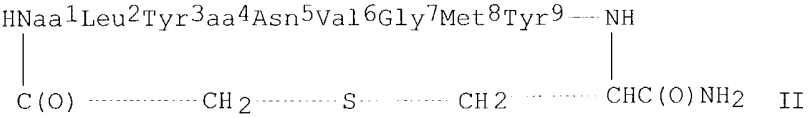


II

AB The invention provides I (L = S, SO, O, CH2; optionally, ≥1 of Tyr3, Glu4, Val6, Met8 and Tyr9 is modified). Also provided is compound II [aa1 = Adi and aa4 = Glu, or each of aa1 and aa4= Adi; L = S, SO, O, CH2; optionally, ≥1 of Tyr3, Val6, Met8 and Tyr9 is modified]. The above compds. (and their conjugates) bind to an SH2 domain in a protein comprising an SH2 domain, are non-phosphorylated, are redox-stable in vivo, and are characterized by an IC50 in vivo of less than about 4.0 <mM with respect to the SH2 domain in Grb2. Upon binding to the SH2 domain of Grb2, a compound as described above has a turn conformation. Optionally, there is a conservative or neutral amino acid substitution at either one or both of Leu2 and Gly7. Also provided are a conjugate comprising a compound as described above and a carrier agent, a composition comprising (i) a compound or a conjugate as described above and (ii) a carrier, a method of inhibiting binding of an SH2 domain in a protein comprising an SH2 domain

to a target protein in an animal, wherein the SH2 domain is contacted with a target protein-binding inhibiting effective amount of a compound or a conjugate as described above, and a method of synthesizing such conjugates.

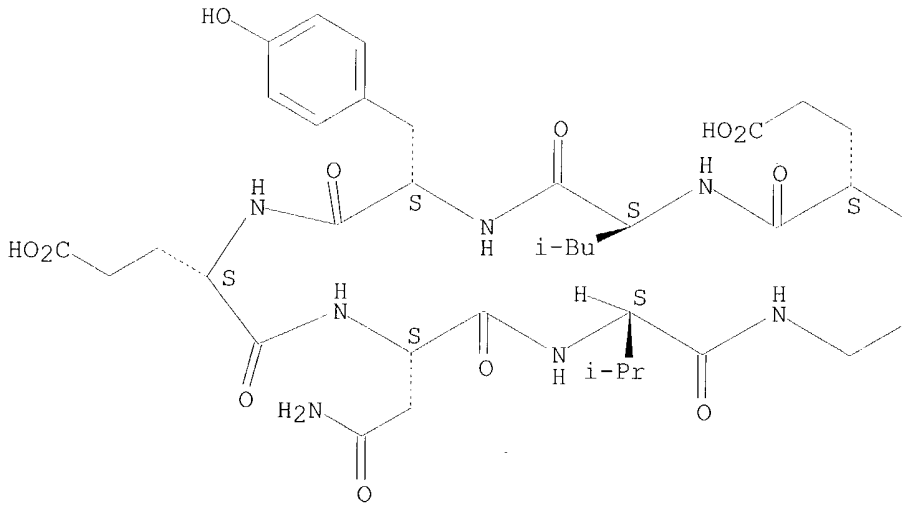
IT **282118-08-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(redox-stable, non-phosphorylated cyclic peptide inhibitors of SH2 domain binding to target protein, conjugates, compns., preparation, and use)

RN 282118-08-5 HCAPLUS

CN L-Cysteinamide, N-(mercaptoacetyl)-L-α-glutamyl-L-leucyl-L-tyrosyl-L-α-glutamyl-L-asparaginyl-L-valylglycyl-L-norleucyl-L-tyrosyl-, cyclic (1→10)-thioether, S-oxide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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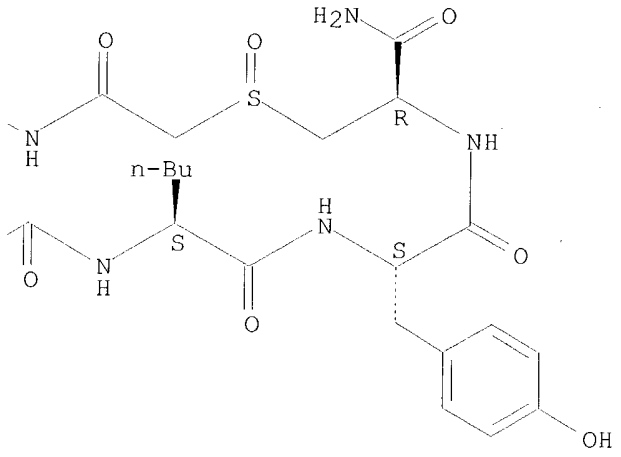

IT **311791-05-6 311791-05-6D**, amino acid-modified derivs. and conjugates **311791-12-5 311791-12-5D**, amino acid-modified derivs. and conjugates **311791-23-8 311791-23-8D**, amino acid-modified derivs. and conjugates
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(redox-stable, non-phosphorylated cyclic peptide inhibitors of SH2 domain binding to target protein, conjugates, compns., preparation, and use)

RN 311791-05-6 HCAPLUS

CN L-Cysteinamide, 4-carboxy-N-(mercaptoacetyl)-L-α-glutamyl-L-leucyl-L-tyrosyl-L-α-glutamyl-L-asparaginyl-L-valylglycyl-L-methionyl-L-tyrosyl-, cyclic (1→10)-thioether, S-oxide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

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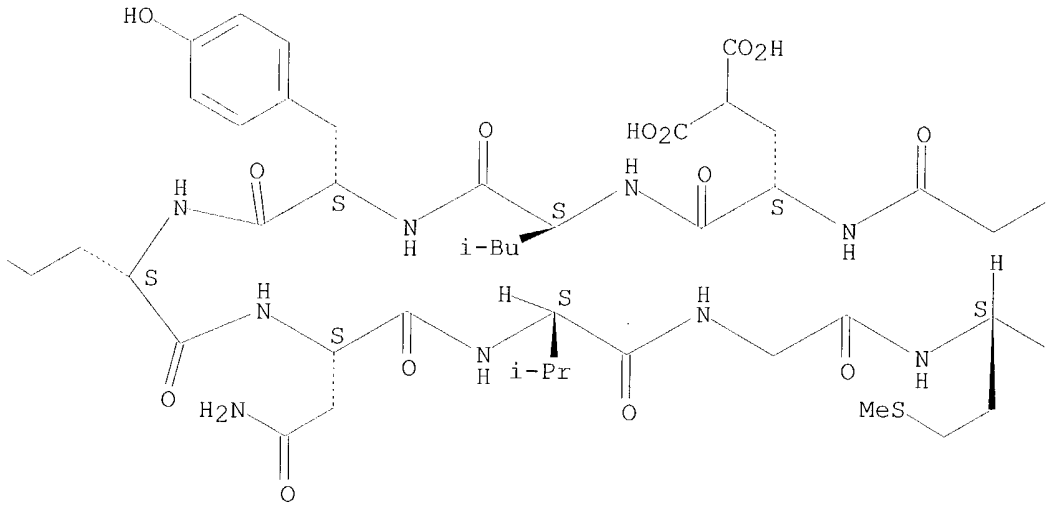

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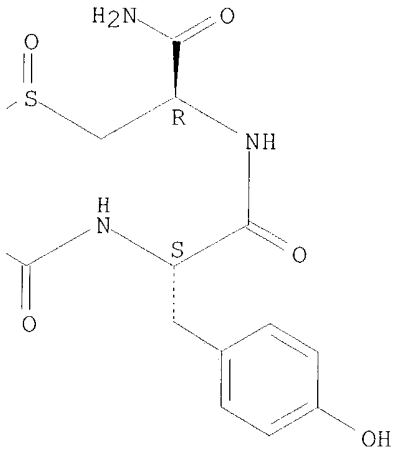


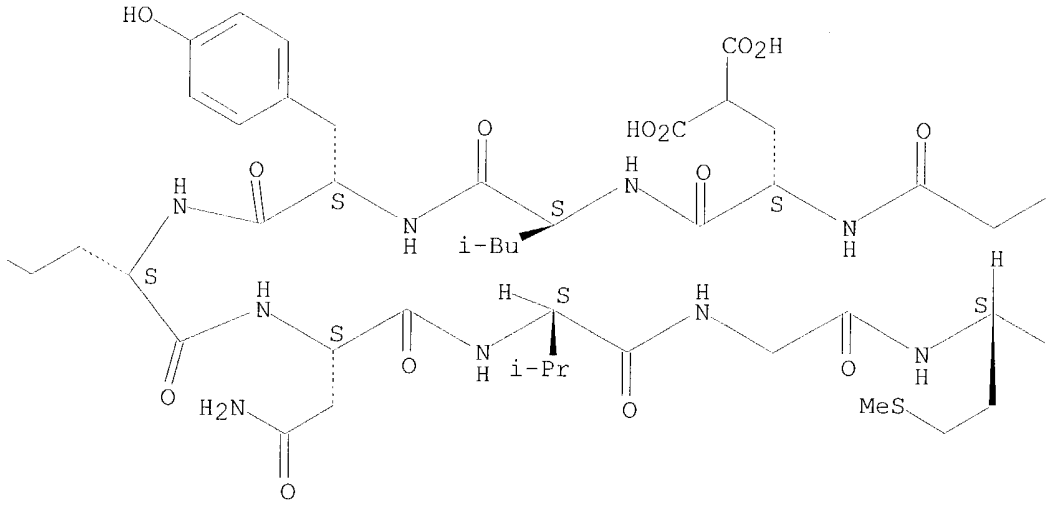
RN 311791-05-6 HCAPLUS
CN L-Cysteinamide, 4-carboxy-N-(mercaptoacetyl)-L-α-glutamyl-L-leucyl-L-tyrosyl-L-α-glutamyl-L-asparaginyl-L-valylglycyl-L-methionyl-L-tyrosyl-, cyclic (1→10)-thioether, S-oxide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

HO_2C

PAGE 1-B



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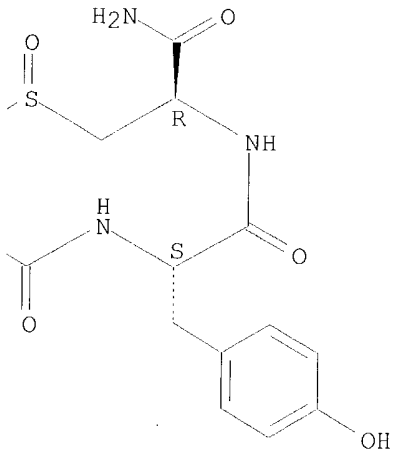

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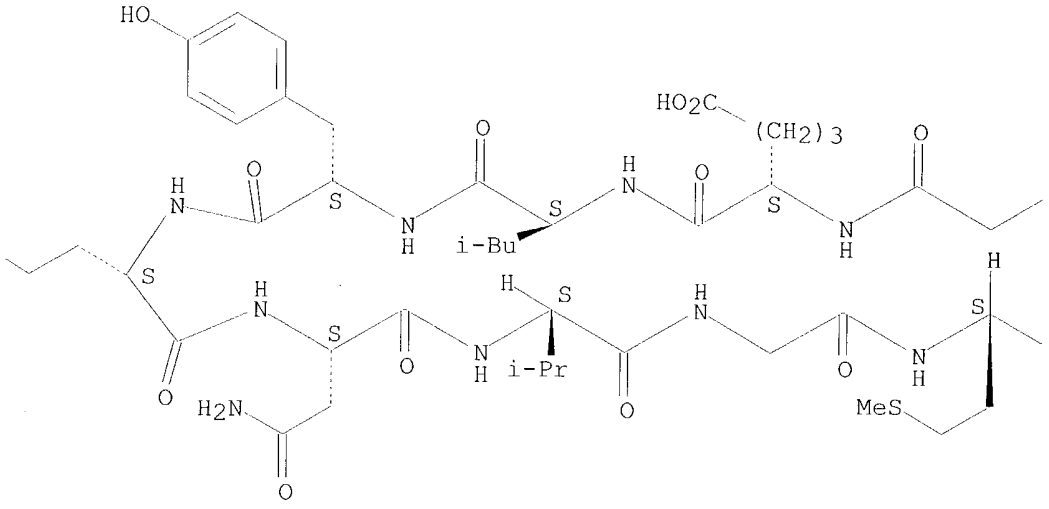
CN L-Cysteinamide, 5-carboxy-N-(mercaptoacetyl)-L-norvalyl-L-leucyl-L-tyrosyl-L-α-glutamyl-L-asparaginyl-L-valylglycyl-L-methionyl-L-tyrosyl-, cyclic (1→10)-thioether, S-oxide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

PAGE 1-B



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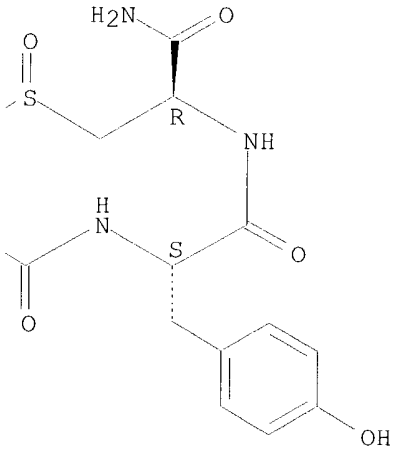

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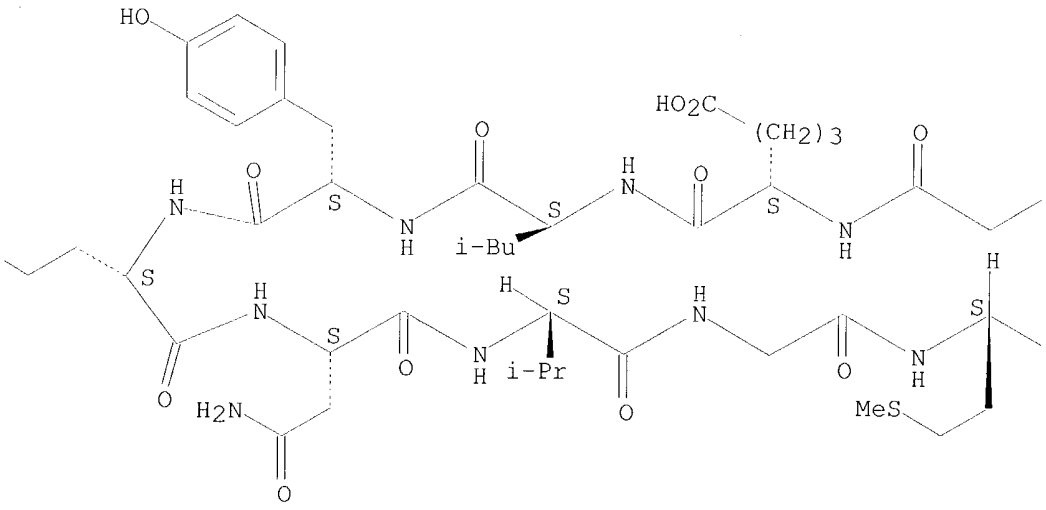
Absolute stereochemistry.

PAGE 1-A

HO_2C

PAGE 1-B



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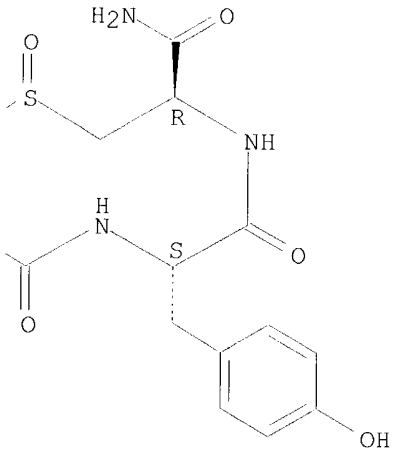

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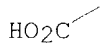
Absolute stereochemistry.

PAGE 1-A



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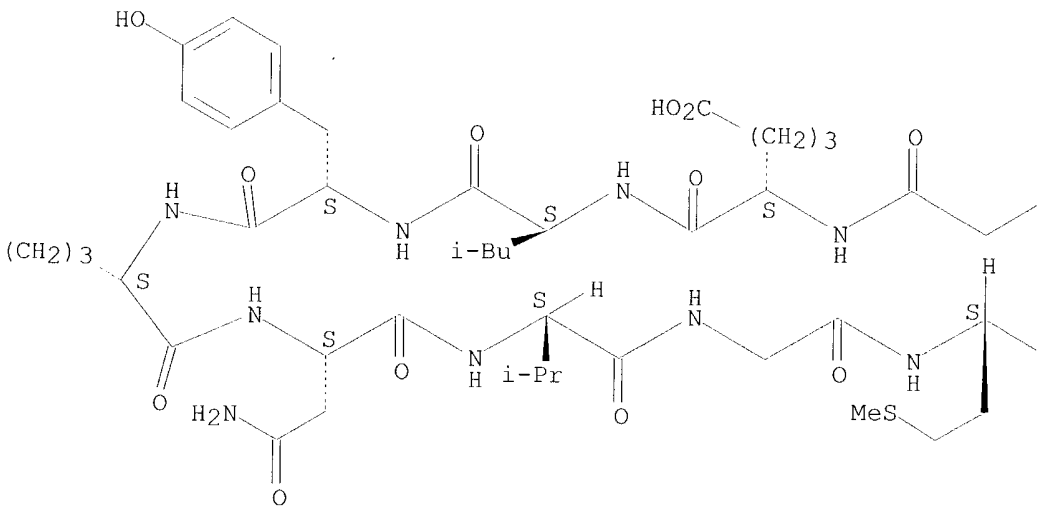

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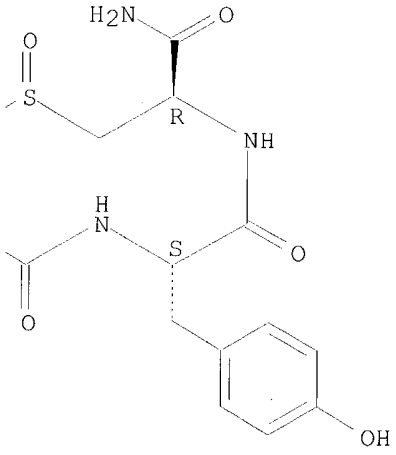

RN 311791-23-8 HCAPLUS
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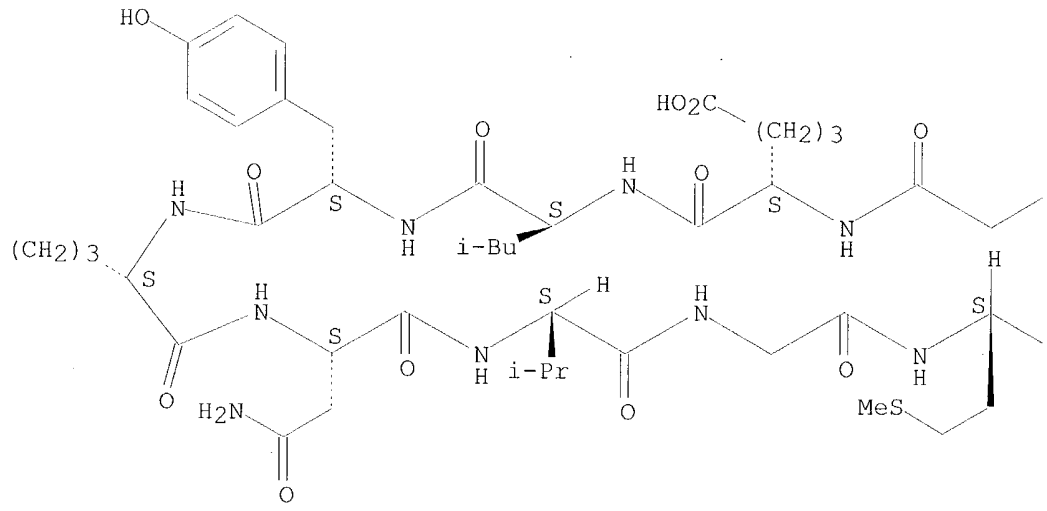
Absolute stereochemistry.

PAGE 1-A

PAGE 1-B



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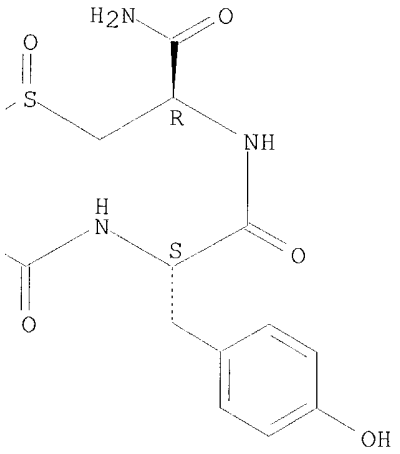


L8 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:288690 HCAPLUS
DOCUMENT NUMBER: 133:84392
TITLE: Structure-activity studies with Grb2-SH2 binding library-based cyclic peptides
AUTHOR(S): Roller, Peter P.; Long, Ya-Qiu; Lung, Feng-Di T.; Voigt, Johannes H.; King, C. Richter
CORPORATE SOURCE: Laboratory of Medicinal Chemistry, National Cancer Institute, NIH, Bethesda, MD, 20892, USA
SOURCE: Peptides 1998, Proceedings of the European Peptide Symposium, 25th, Budapest, Aug. 30-Sept. 4, 1998 (1999), Meeting Date 1998, 706-707. Editor(s): Bajusz, Sandor; Hudecz, Ferenc. Akademiai Kiado: Budapest, Hung.
CODEN: 68WKAY
DOCUMENT TYPE: Conference
LANGUAGE: English

AB A report from a symposia exploring the salient mol. features required for binding the redox-stable thioether cyclized analog G1TE to the GRb2-SH2 and on development of G1TE analogs with higher binding affinities. G1TE analogs prepared with substitutions at the Glu1, Tyr3 and Glu4 positions, as well as at the thioether linkage site, were evaluated using Fmoc chemical methodol. Substitutions by various amino acids were incorporated into the G1TE analogs, including L-2-aminoadipic acid, which has a CH2-extended sidechain compared to Glu. Overall, the results indicate that the cyclized structure of nonphosphorylated G1TE is necessary for retention of its binding affinity to Grb2-SH2 and that this discovery, assisted by structure based design, should lead to the development of nonphosphorylated, highly potent and specific inhibitors of Grb2/growth factor (GF) receptor interactions for use in cells over-expressing GF receptors.

IT **282118-08-5P**
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PREP

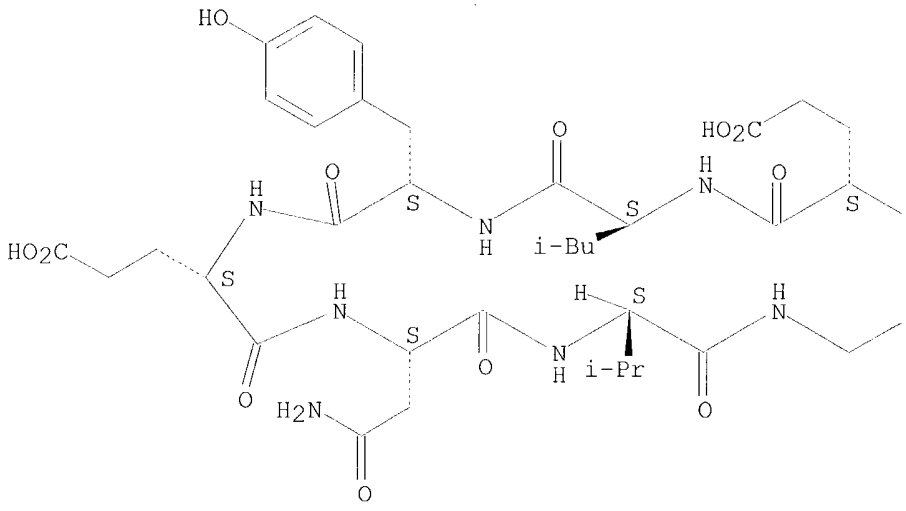
(Preparation); PROC (Process)
(structure-activity studies with GRB2-SH2 binding library-based cyclic peptide G1TE analogs)

RN 282118-08-5 HCAPLUS

CN L-Cysteinamide, N-(mercaptoacetyl)-L-α-glutamyl-L-leucyl-L-tyrosyl-L-α-glutamyl-L-asparaginyl-L-valylglycyl-L-norleucyl-L-tyrosyl-, cyclic (1→10)-thioether, S-oxide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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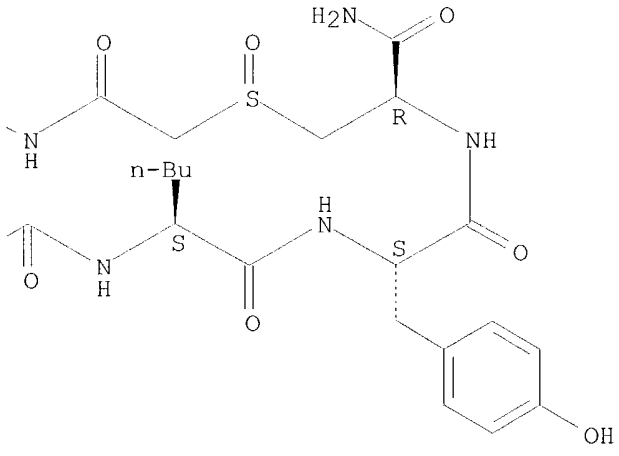

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT